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A novel syndrome involving primary skeletal growth and retardation in siblings

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An identical pattern of malformations was found in two brothers both having microcephaly and severe developmental delay. Additionally, they had hypotelorism, epicanthic folds, and convergent strabismus. There was shortening of either the radius or the tibia and shortening of the first metacarpals. Persistently dorsally flexed fingers and toes were noted, all of which are unusually long. Both boys had a high-pitched voice and were unable to communicate verbally at the age of 4.5 years. They both developed short stature. One brother has anal atresia; the other had a pulmonary artery atresia, VSD, ASD, and an over-riding aorta. This apparently new syndrome is possibly an autosomal, or a X-linked recessive trait.
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Keywords: short stature, microcephaly, mental retardation, high-pitched voice, long fingers and toes, carp-shaped mouth, strabismus, hypoplastic radius, hypoplastic tibia

INTRODUCTION

We report a northern Italian family, consisting of three boys, the oldest of whom is normal while the other two brothers suffered identical patterns of malformations with microcephaly and developmental delay.

CASE REPORT 1

The second son of unrelated parents was spontaneously delivered in the 41st week of pregnancy weighing 2030 g (– 3 SD), 49 cm (– 0.7 SD) long, with a head circumference of 30 cm (– 5 SD). He had a 'crowded' face, his ears were low-set with marked posterior angulation, a low anterior hair line, hypotelorism, and bilateral epicanthic folds. His eyes were normal with severe convergent strabismus. His nose had a prominent nasal bridge and the mouth was 'carp-shaped' (Figure 1). There was a high-arched palate with a prominent median palatal raphe which followed the line of fusion of the hard palate. There was significant microcephaly (30 cm head circumference, – 5 SD). The right tibia and first metacarpal were both hypoplastic and there were bilateral dorsally flexed fifth toes causing impaired movement of both extremities (Figure 2). His fingers and toes were unusually long. In addition, he had severe congenital heart anomalies (pulmonary atresia combined with VSD, ASD, and over-riding aorta).

The results of repeated analyses of blood and urine for quantitative amino acids and organic short-chain fatty acids, and lactate, indicating inborn errors of metabolism were within the normal range. There was no evidence of prenatal infections (Rubella, Toxoplasma, CMV, Syphilis, and HSV).

During the first 4 years of life he failed to thrive which resulted in short stature with body weight and length below the first percentile. His height was 86 cm (– 4 SD), weight 9.5 kg (– 4 SD), and head circumference 46 cm (– 4 SSD). No brain malformations could be detected by MRI and ultrasound examinations. There was an unusually high-pitched voice. At 4.5 years of age, he was still unable to communicate verbally. Shortly, before his fifth birthday, he died of decompensated heart failure; his parents refused an autopsy.

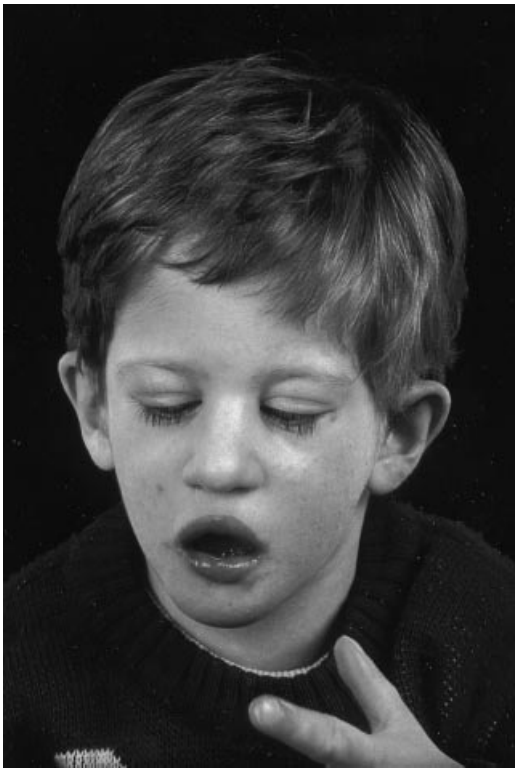

FIGURE 1. Case 1 at 4.2 years of age with unusual facial features, low-set ears, strabismus and "carp" mouth

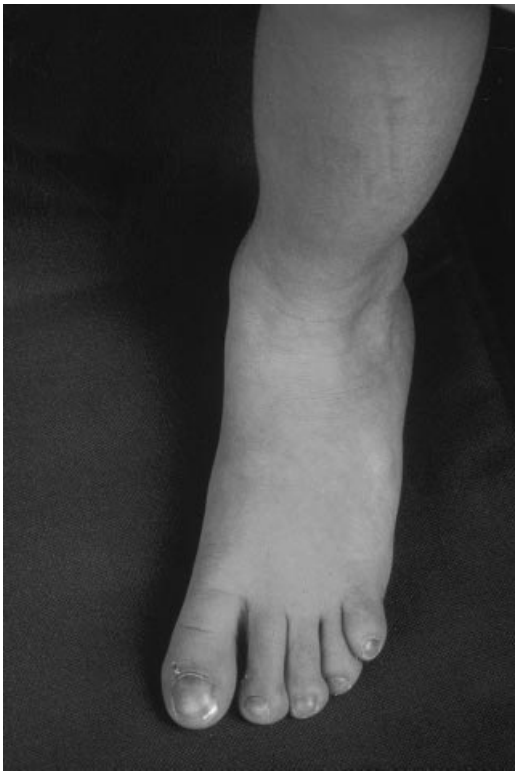

FIGURE 2. Foot of Case 1 with long toes and dorsally flexed 5th toe; as well as clubbing of nails due to heart failure

CASE REPORT 2

The third child, a boy, was delivered by cesarean section in the 41st week of pregnancy weighing 2270 g (– 2 SD) and 45 cm long (– 2 SD). He had a microcephalic head with a circumference of 31.7 cm (– 4 SD). His facial features were similar to his brother Figures 3 and 4). In addition, he had bilateral ptosis (the left > right) and bilateral renal hypoplasia visualized by ultrasound with normal renal function. In addition, he had an imperforate anus. A bilateral vesico-ureteric reflux spontaneously resolved during the second year of life. Blood and urine examinations similar to his brother related to inborn errors of metabolism and prenatal infections were normal. No brain malformations could be detected by ultrasound examinations. His heart was normal. His left elbow remained bent due to dislocation of radial head; additionally, the 2nd fingers (Figure 5) and 5th toes bilaterally were persistently flexed dorsally.

His severe mental and developmental retardation have persisted. His voice is also extremely high-pitched and his verbal communication is rudimentary at 5 years of age. His body weight at 6 years of age was 12 kg (– 4 SD), height: 100 cm (– 4 SD) and head circumference 52.3 (– 4 SD).

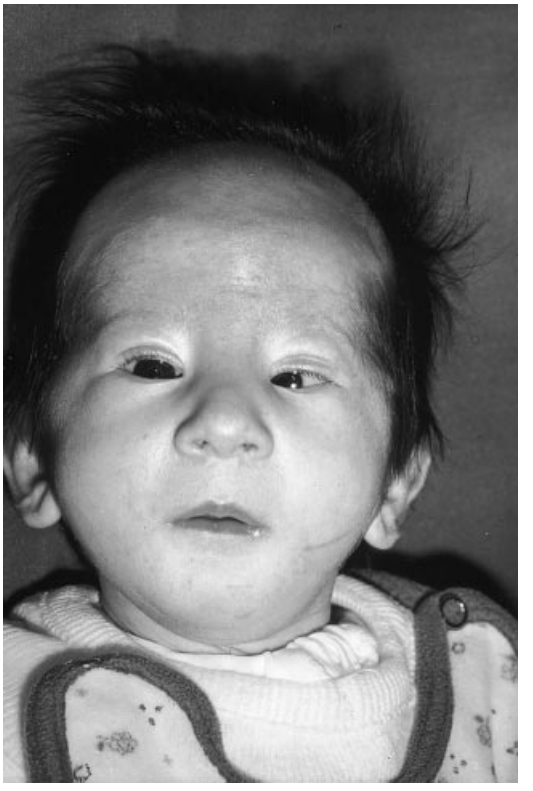

FIGURE 3. Case 2 at 3 months of age. Facial features similar to those of his brother: strabismus, prominent nasal bridge, 'carp' mouth and low-set ears

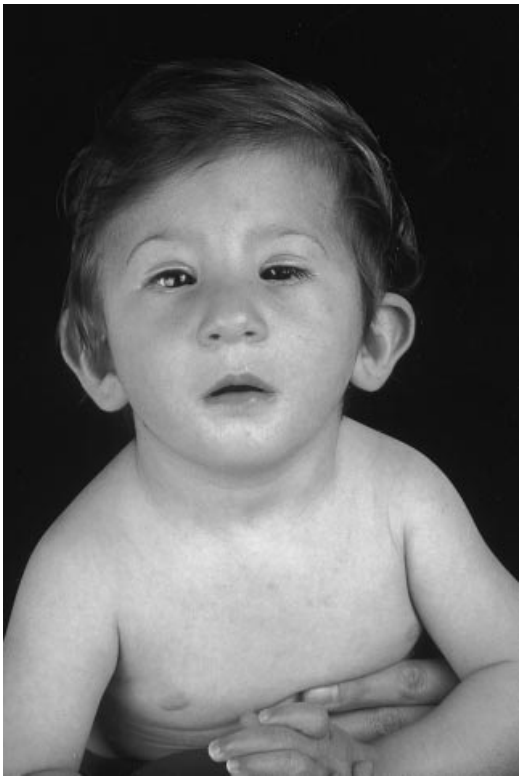

FIGURE 4. Case 2 at 3 years of age

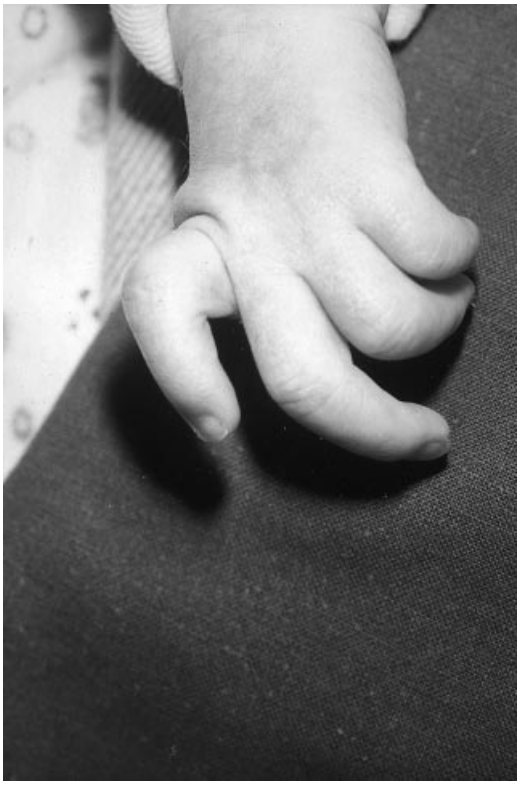

FIGURE 5. Extension of the 2nd finger (Case 2)

CYTOGENETIC STUDIES

The first chromosomal analysis of Case 1 was carried out when he was 11 months old, and it was repeated 3 months later. GTG-banding with an average resolution of 450–500 bands per haploid set (ISCN, 1995) revealed no indication of numerical or structural chromosomal aberrations. In order to screen for structural changes involving the telomeres (e.g. translocations) beyond the resolution of conventional banding techniques, a chromosome arm-specific subtelomeric fluorescence *in situ* hybridization probe set (Chromoprobe-T; cytocell, Adderbury, UK) was used. There was no indication of a loss or exchange of regions detectable by these probes. The first chromosomal analysis of the younger brother (Case 2) was obtained prenatally from a chorionic villus sampling. QFA-banding with a resolution of about 400 bands was used. Shortly after birth, the examinations were repeated using GTG-bands with an average resolution of 450 bands. No chromosomal abnormalities were discovered in either analysis. There were no chromosomal anomalies in either parent following two independent chromo-

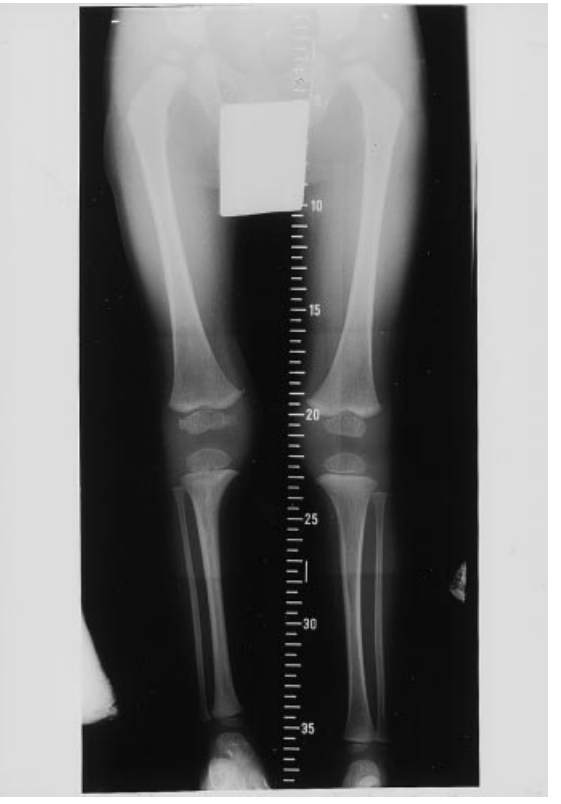

FIGURE 6. Radiograph of both legs (Case 1), hypoplastic right tibia (see text), Additionally, broad, partially fragmented, distal right femoral epiphysis, significant narrowing of the medullary cavity of the right tibia; mild shortening of the right fibula

somal analyses of GTG-banding with resolutions around 500 bands.

RADIOLOGICAL FINDINGS

Case 1 had a shorter right tibia with a significant narrowing of its medullary cavity: right tibia, 13.5 cm; left tibia: 14.5 cm (Figure 6). Additionally, a slight shortening of the right fibula was observed: right: 11.3 cm vs left: 12.0 cm. Case 1 had a broad, particularly fragmented, right distal femoral epiphysis. Both hands had a short hypoplastic 1st metacarpal and slight shortening of digit V including metacarpal V (Figure 7).

Case 2: both hands had a short first metacarpal with a distal pseudoepiphysis. The left hand had a peculiar malformation of middle phalanx V with a cone-shaped epiphysis and 'Christmas angel' shape (Figure 8). Additionally, there was a shortening of the left radius at the proximal end as well as dislocation of the radial head (Figure 9).

DISCUSSION

The two brothers have relatively non-specific malformations that have been described in several syndromes: low birth weight, prenatal onset of short stature with microcephaly, short hypoplastic metacarpals, and delayed bone age. However there are more specific abnormalities that appear to add up to a novel syndrome. These include low-set posteriorly rotated ears, stabismus, 'carp' mouth, ptosis, long fingers and toes, high pitched voice, heart defects, and anal atresia. The inheritance of the condition is possibly X-linked or autosomal recessive, although a small cryptic chromosomal rearrangement cannot be ruled out.

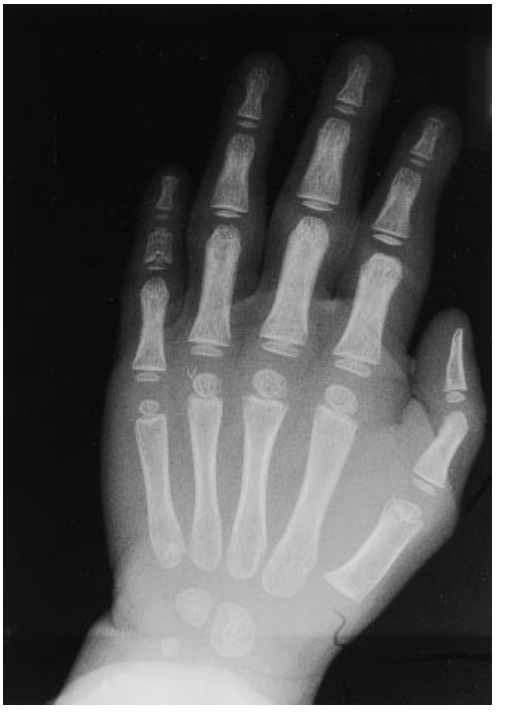

FIGURE 8. Left hand (Case 2): short first metacarpal with distal pseudoepiphysis, malformation of middle phalanx V with cone-shaped epiphysis and 'Christmas angel' shape

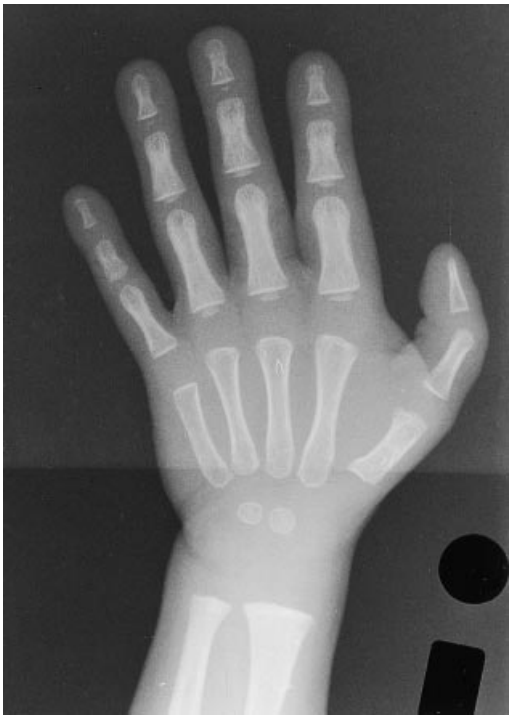

FIGURE 7. Left hand (Case 1); hypoplastic 1st metacarpal; slight shortening of digit V including metacarpal V

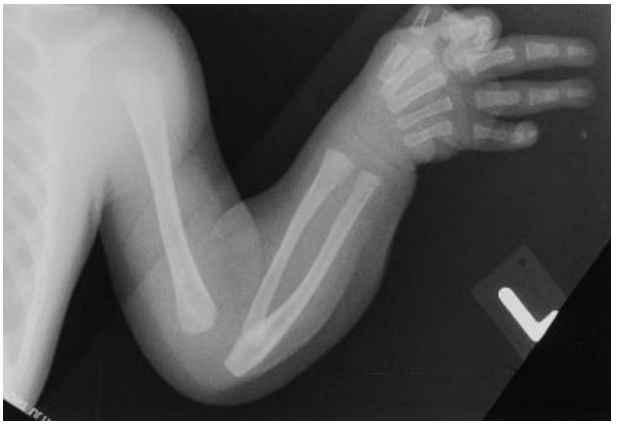

FIGURE 9. Shortening of the left radius at the proximal end; as well as dislocation of radial head (Case 2)